Figure 1

The Cholesterol, Fatty Acid and Phospholipid Pathways:

Regulation by Sterol Regulatory Element Binding Proteins (SREBPs)

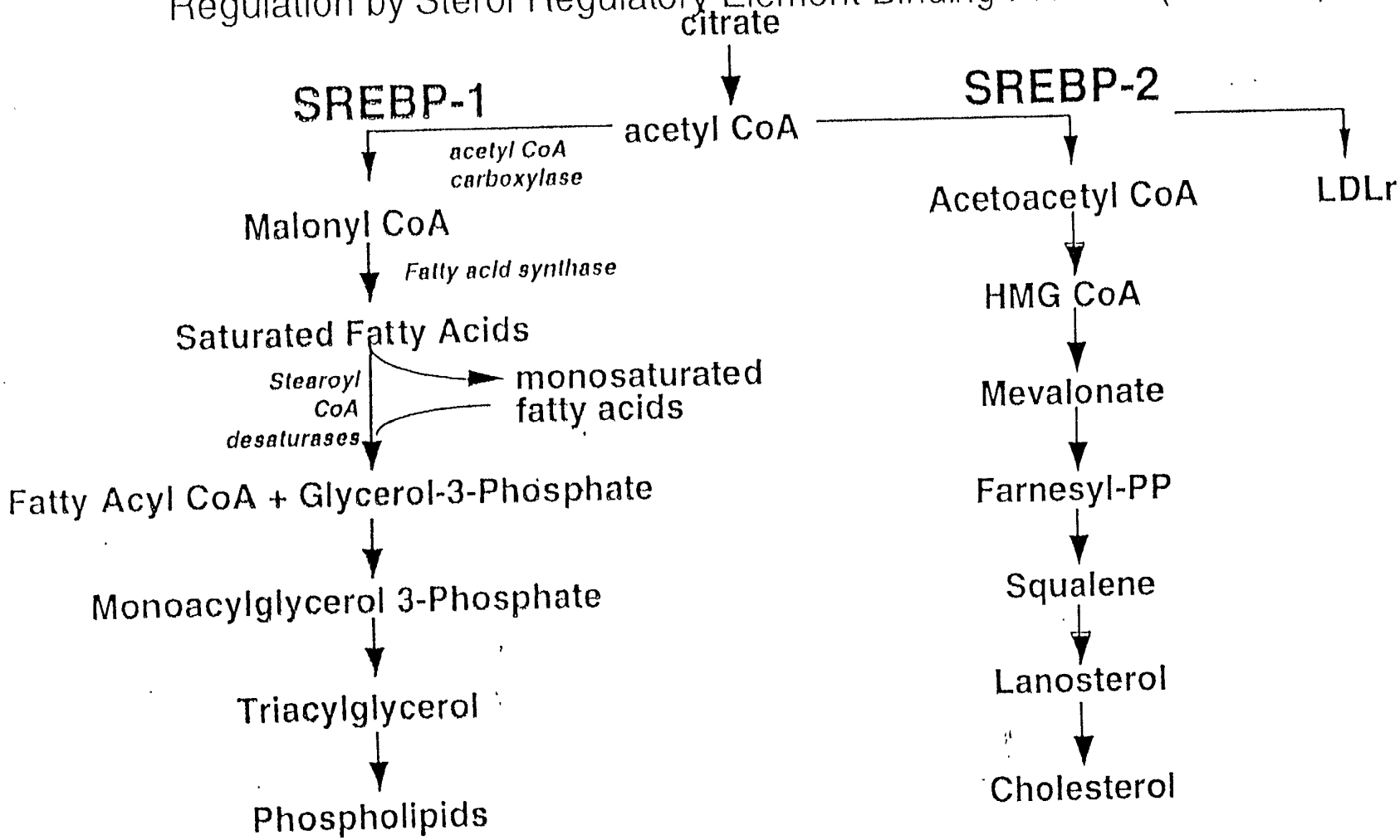


Figure 2

24.25-epoxy cholesterol activate SREBP1 and FAS

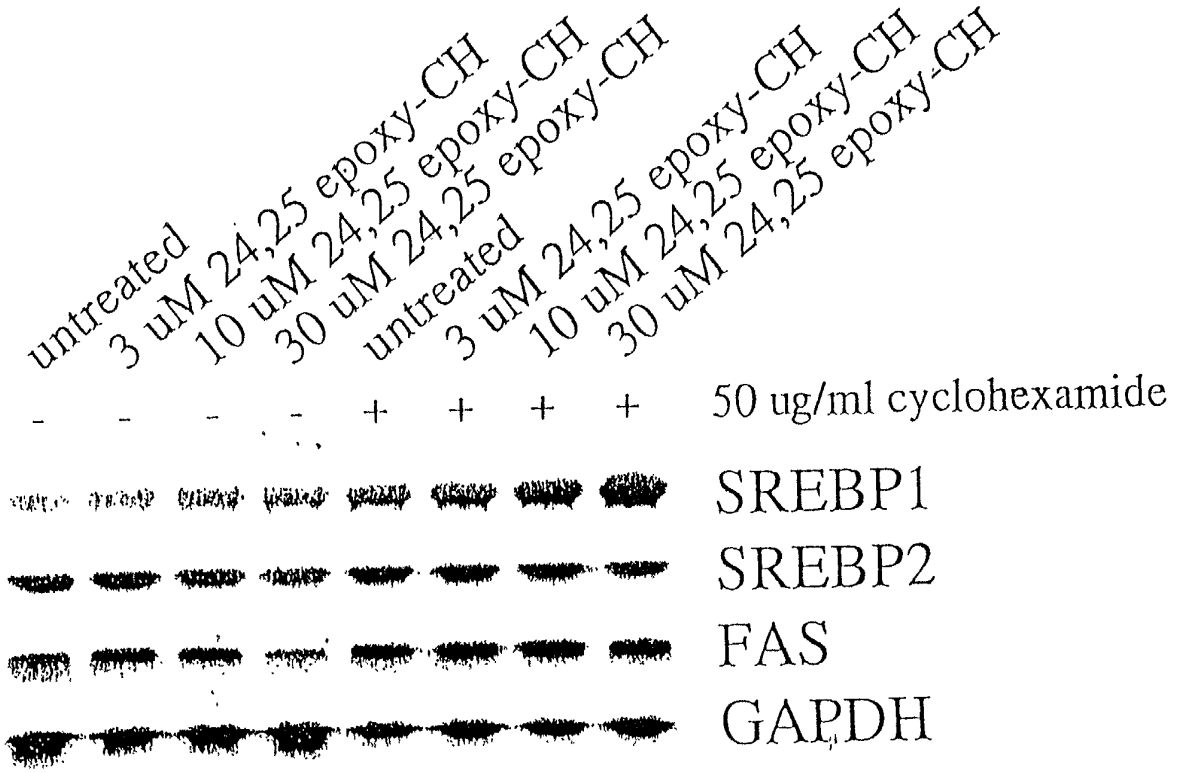


Figure 3

24,25 epoxy-cholesterol activates SREBP1 in different cell lines

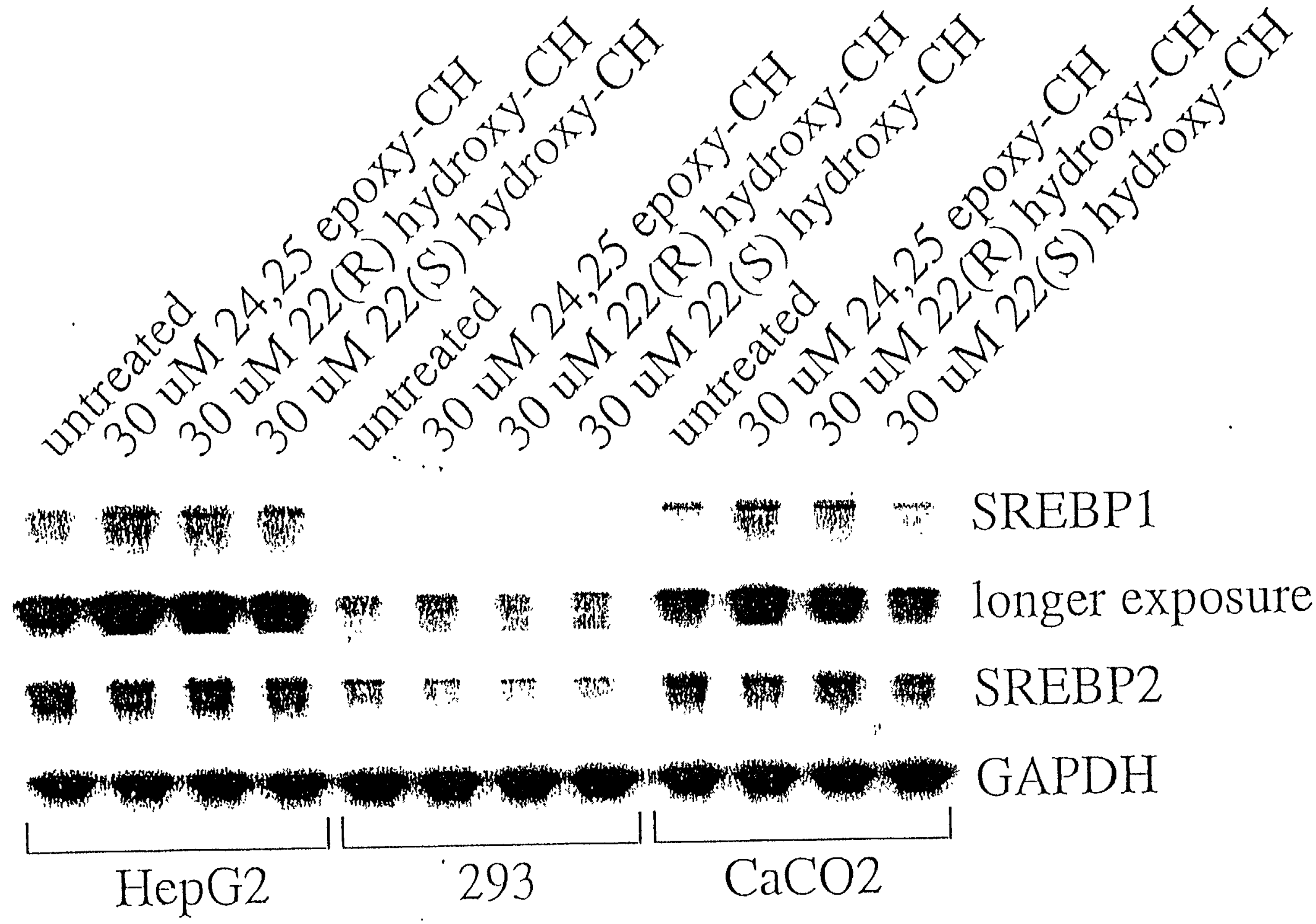


Figure 4

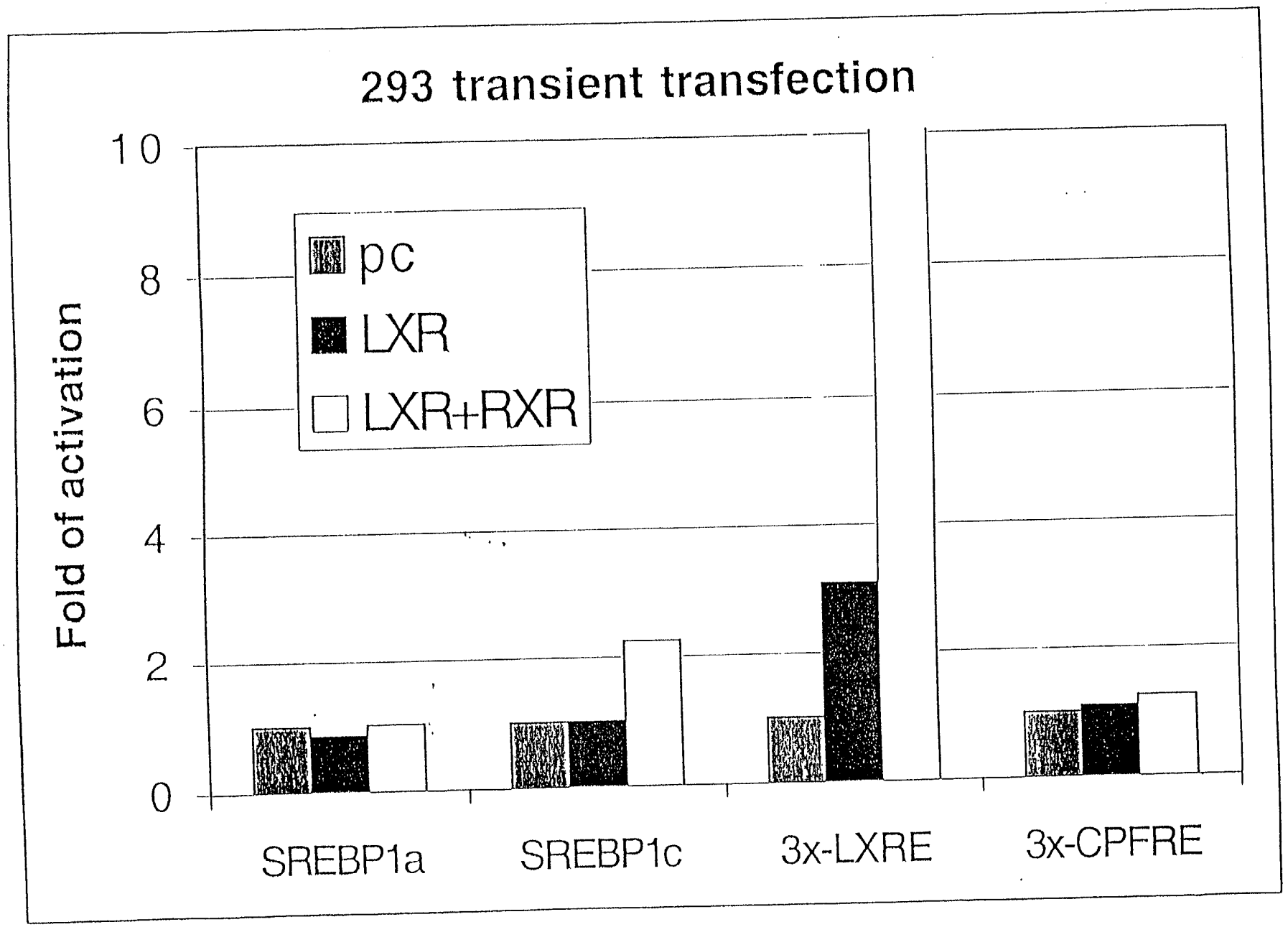
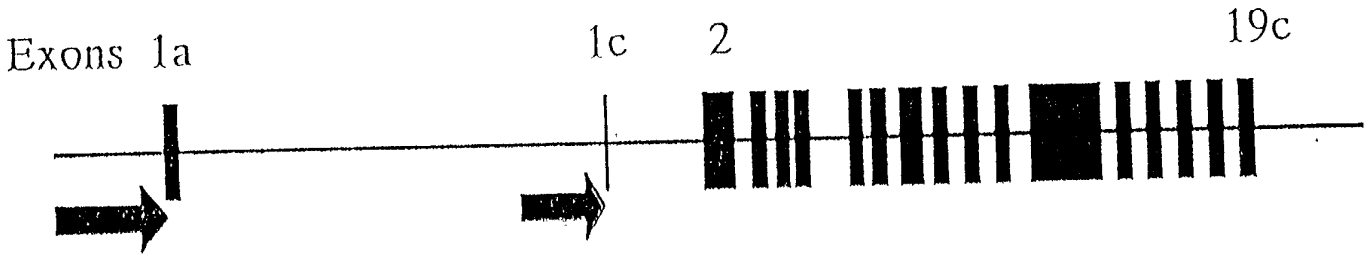

293 transient transfection
Fold of activation
10
8
6
4
2
0
pc
LXR
LXR+RXR
SREBP1a
SREBP1c
3x-LXRE
3x-CPFRE

Figure 5

LXR sites on SREBP1



Human SREBP1c promoter

CATGTGGGACCTGCCTGGCATGTGGAAGGGGCTTGGGGTGCAGCTGTGTCCCTGGCCCCAGCACTGCCACACCCCTCGGT

ACCTTGACCTCACTTTTGCGCTCTGGAGGGCAGAACCTCTGAGCCAGCTCTCAGGGATACCTTTTTTCCTCGATGGCCTT

TTCTGGGAACTGCCCTCGCCTGCTATCTCTGAGCCCTGCCTGCCCTTCCCCCAAAGCCATCATAGACCCCTACCTCCTAT

CCAGATGGAGCCTGGCCATGGAATGCTTGGGGTGAGAGGGACCCATAGCGGGCTCCGGGCATTGTTAGGGGGCTAGGTGG

TGTCTGCAGAGGCCCCACCTGTGGCAGGGTTTACATGCCGCCACCCCTGCCCTCCTCTTGGGTAGCTGGGGTCAGAAGGG

CCTGAGGCCTCACTCTCTCTGCATCTTAGTTTCTTCACATCTAAAATGCTATTCATATGCCTGCCTGAGGGTGGTTGGGG

CCTCCGTGCAGTAAGTGGAGAGAAGCCTTCAGCCAGAGGACCCCCATATGCTTAAACATCCAGACACCAAGGGCCACTCA

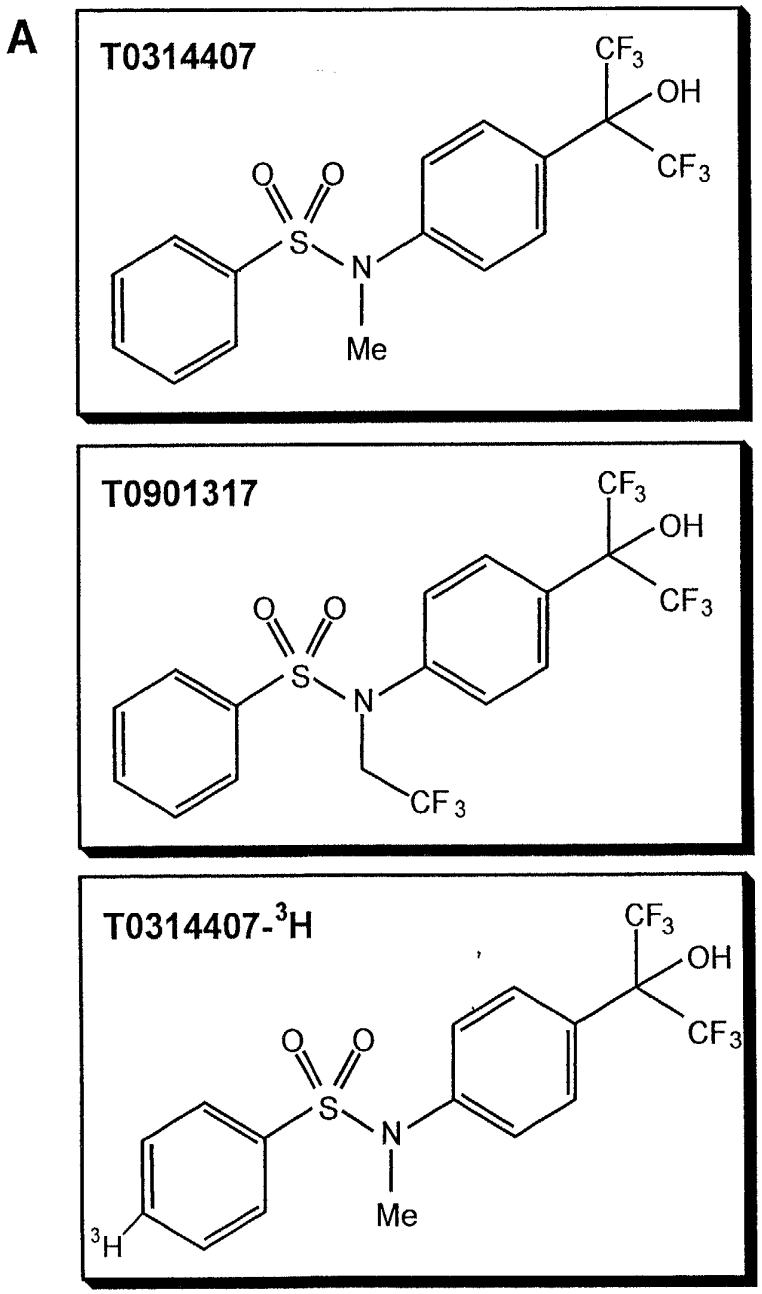
CAGACAGCAGCCGGCTTGTGTTTCGTCATCCCTTTTGGGTCAGGAACTGGGGACGCTGGACTCCAGATCTCCAGGAGGCC

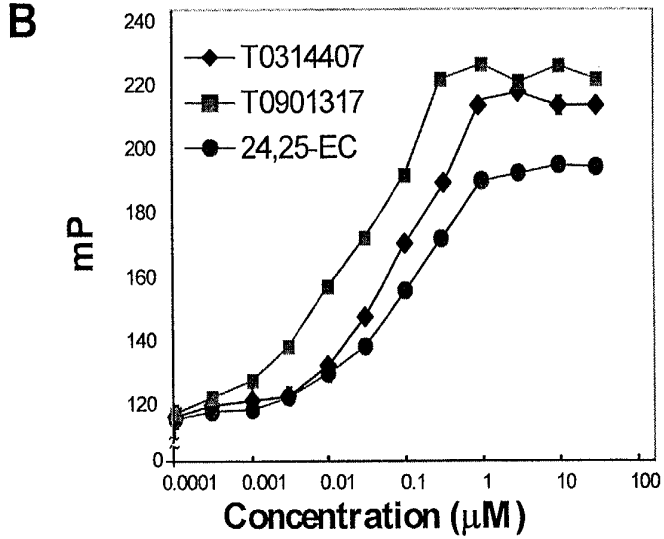
ATCCCAGACTAGGCGGGAAGGAGGCCTCAGCCCTGAGCTGAAAACCTGAAATTCTAGAATAAACCCCAGGCCCCACTCCC

AGCATGGGCAGCGGGGAGGGGTAGGGCCAACGGCCTGGACGCCCCAAGGGCGGGCGCAGATCGCGGAGCCATGGATTGCA

CTTTCGAAGgtatttttggaggcctccccac

Figure 6


A
T0314407
CF3
OH
CF3
O
O
S
N
Me
T0901317
CF3
OH
CF3
O
O
S
N
CF3
T0314407-3H
CF3
OH
CF3
O
O
S
N
Me
3H


B
240
220
200
180
160
140
120
0
mP
T0314407
T0901317
24,25-EC
0.0001
0.001
0.01
0.1
1
10
100
Concentration (μM)

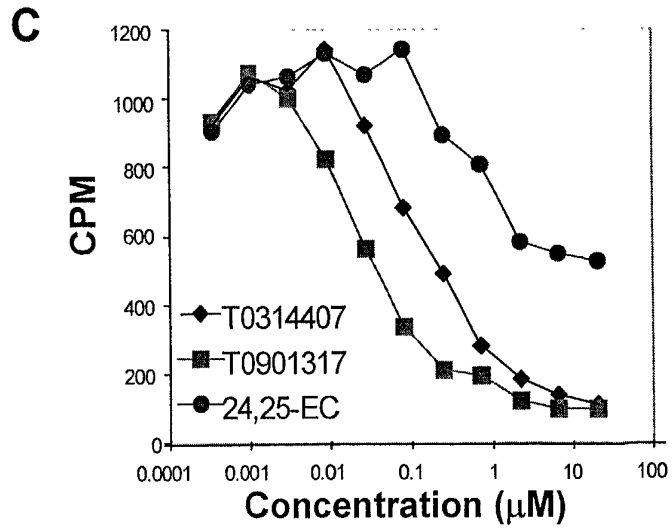

C
1200
1000
800
600
400
200
0
CPM
T0314407
T0901317
24,25-EC
0.0001
0.001
0.01
0.1
1
10
100
Concentration (μM)

Figure 7

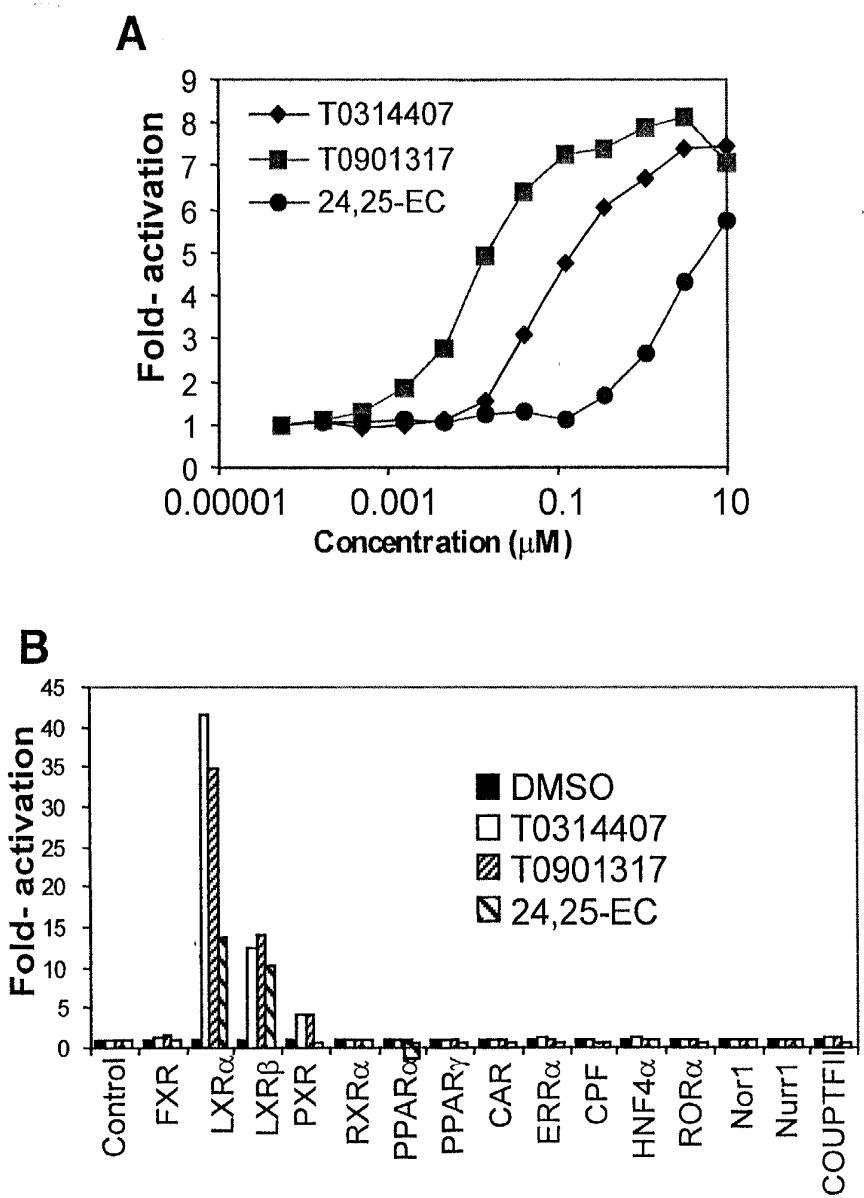
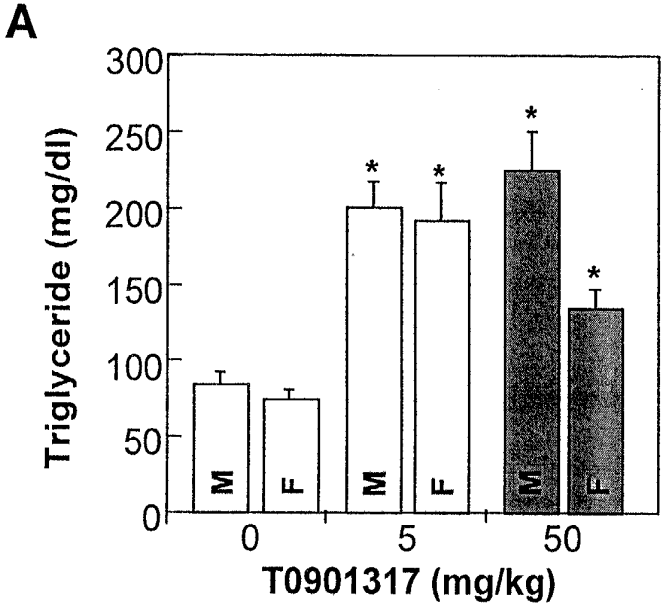
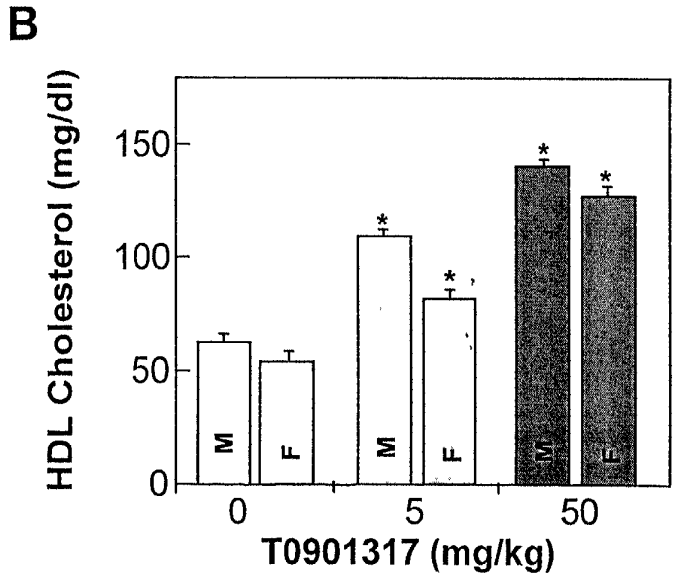
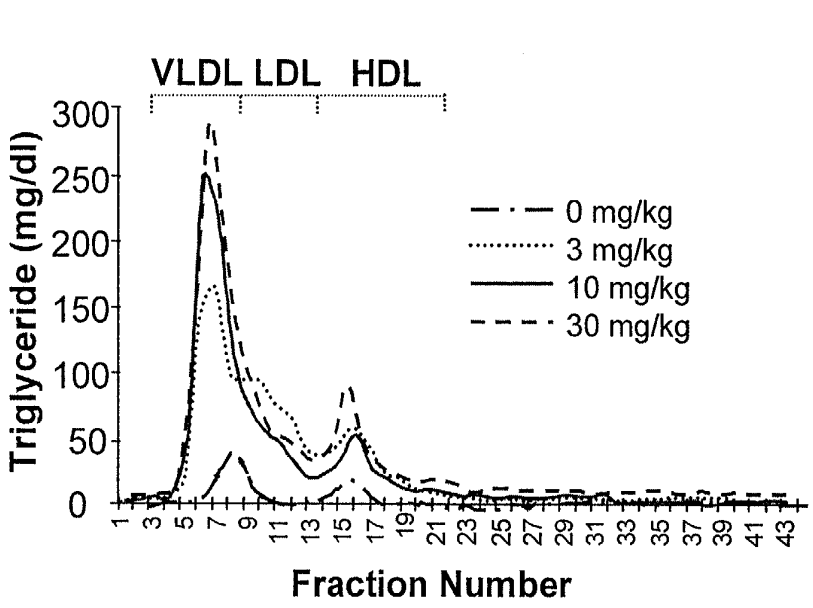
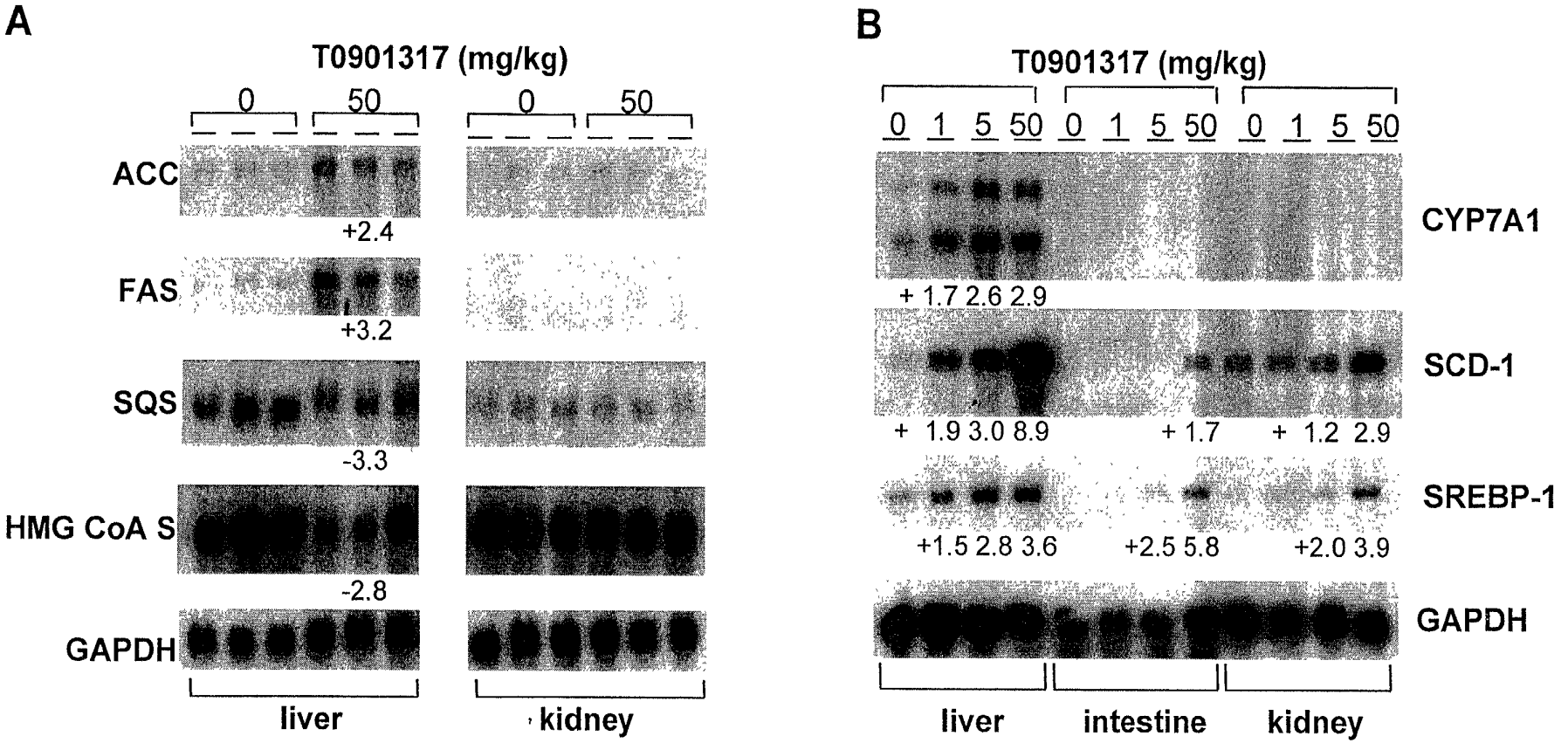

A
Fold- activation
T0314407
T0901317
24,25-EC
Concentration (μM)
B
Fold- activation
DMSO
T0314407
T0901317
24,25-EC
Control
FXR
LXRα
LXRβ
PXR
RXRα
PPARα
PPARγ
CAR
ERRα
CPF
HNF4α
RORα
Nor1
Nurr1
COUPTFII

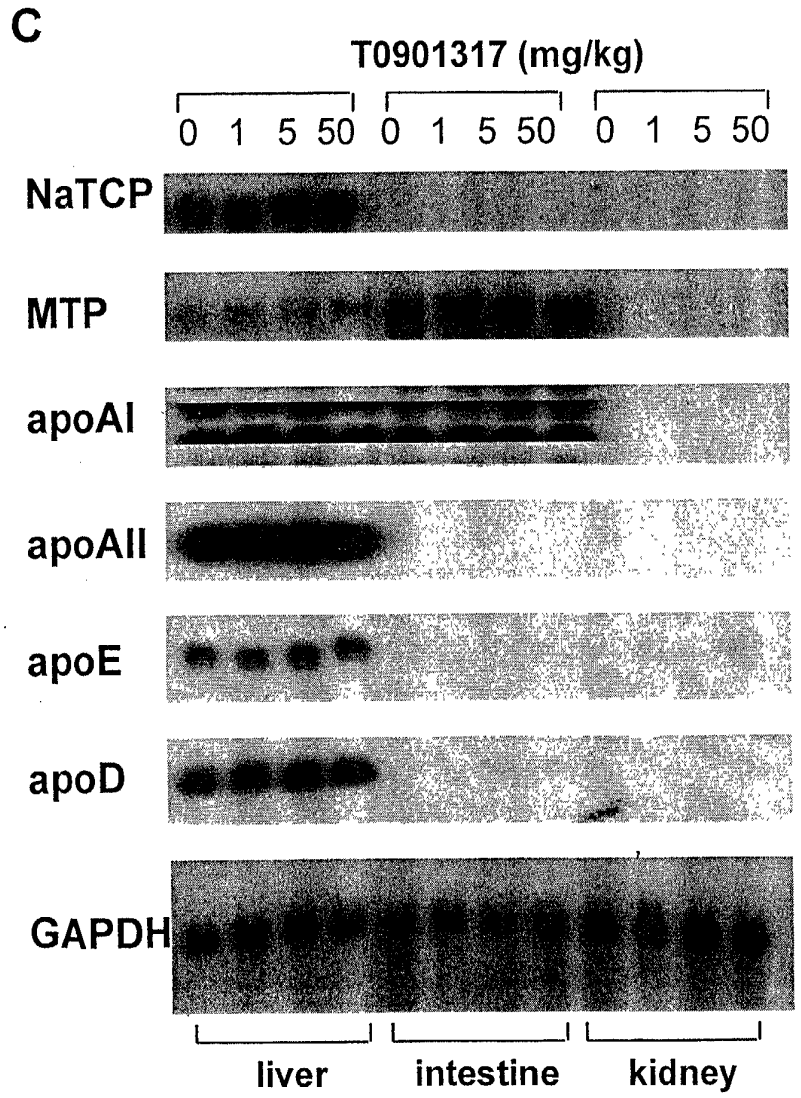
Figure 8

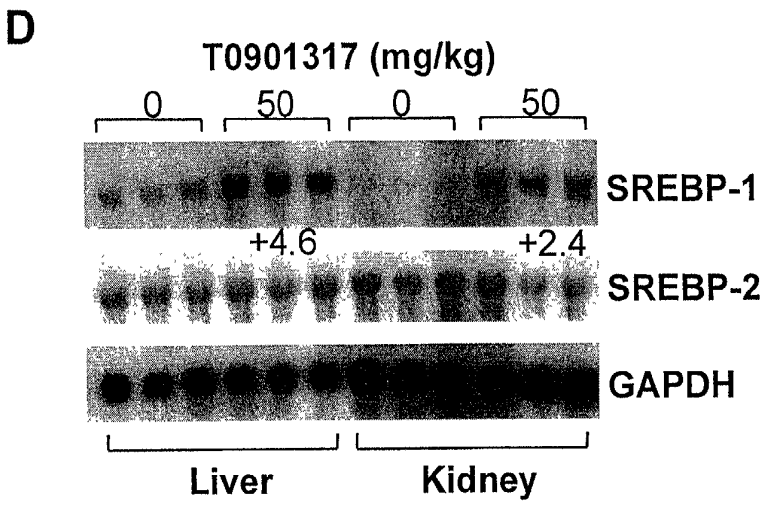

A
Triglyceride (mg/dl)
300
250
200
150
100
50
0
M
F
M
F
M
F
*
*
*
*
0
5
50
T0901317 (mg/kg)


B
HDL Cholesterol (mg/dl)
150
100
50
0
M
F
M
F
M
F
*
*
*
*
0
5
50
T0901317 (mg/kg)


C
VLDL LDL HDL
Triglyceride (mg/dl)
300
250
200
150
100
50
0
0 mg/kg
3 mg/kg
10 mg/kg
30 mg/kg
1
3
5
7
9
11
13
15
17
19
21
23
25
27
29
31
33
35
37
39
41
43
Fraction Number


A
T0901317 (mg/kg)
0
50
0
50
ACC
+2.4
FAS
+3.2
SQS
-3.3
HMG CoA S
-2.8
GAPDH
liver
kidney
B
T0901317 (mg/kg)
0 1 5 50 0 1 5 50 0 1 5 50
CYP7A1
+ 1.7 2.6 2.9
SCD-1
+ 1.9 3.0 8.9
+ 1.7
+ 1.2 2.9
SREBP-1
+1.5 2.8 3.6
+2.5 5.8
+2.0 3.9
GAPDH
liver
intestine
kidney


C
T0901317 (mg/kg)
0 1 5 50 0 1 5 50 0 1 5 50
NaTCP
MTP
apoAI
apoAII
apoE
apoD
GAPDH
liver
intestine
kidney


D
T0901317 (mg/kg)
0 50 0 50
SREBP-1
+4.6
+2.4
SREBP-2
GAPDH
Liver
Kidney

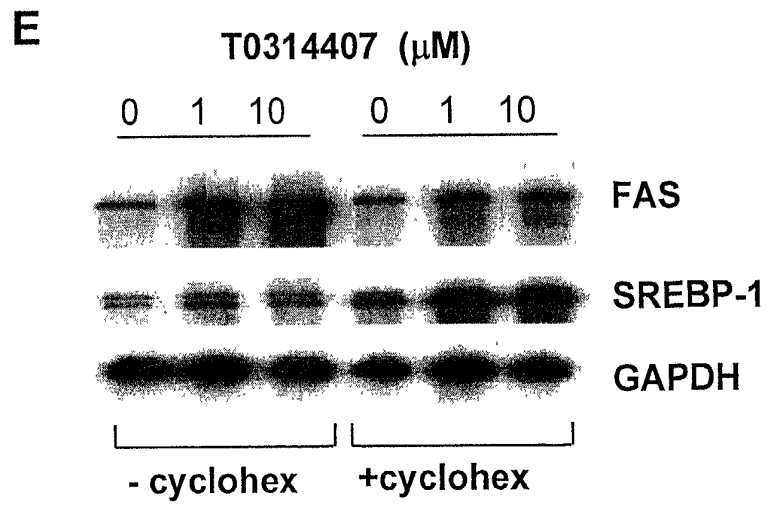

E
T0314407 (μM)
0 1 10 0 1 10
FAS
SREBP-1
GAPDH
- cyclohex
+cyclohex

Figure 10

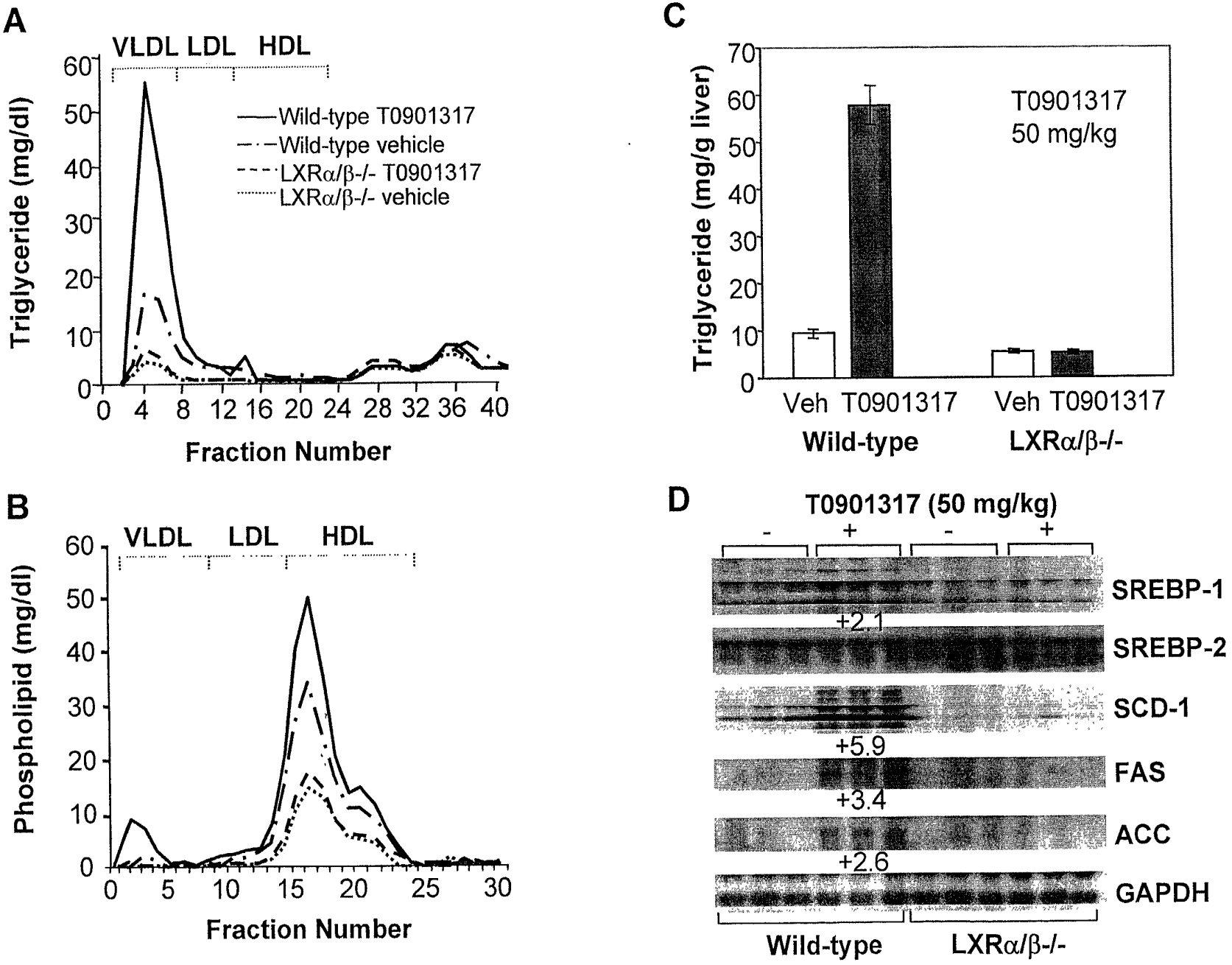

A
VLDL LDL HDL
Triglyceride (mg/dl)
Wild-type T0901317
Wild-type vehicle
LXRα/β-/- T0901317
LXRα/β-/- vehicle
Fraction Number
B
VLDL LDL HDL
Phospholipid (mg/dl)
Fraction Number
C
Triglyceride (mg/g liver)
T0901317
50 mg/kg
Veh T0901317 Veh T0901317
Wild-type LXRα/β-/-
D
T0901317 (50 mg/kg)
- + - +
SREBP-1
+2.1
SREBP-2
SCD-1
+5.9
FAS
+3.4
ACC
+2.6
GAPDH
Wild-type LXRα/β-/-

Figure 11

Supplementary Table I. The sequence of PCR primers used for amplifying mouse cDNA probes

cDNA Probe	Primer Set	Primer Sequence	PCR Product Length
acetyl CoA carboxylase	5’	TACCTGTGGGACAGCAACCA	521
	3’	TGGTCGACAGCAAGGGAA	
fatty acid synthase	5’	CCCGATGGGGGTTTCATC	493
	3’	GATCCCTCTGGGTGTCCC	
squalene synthase	5’	CGTGCAGTGCTTGAATGAACT	288
	3’	TTGGGGATCCGGTGATAAAT	
HMG CoA synthase	5’	CCCAGCAGAGGTTTTCTACAA	1285
	3’	AATTCCTCAGGGGACATGC	
SREBP-1	5’	TCA ACAACCAAGACAGTGACTTCCCTGGCC	1028
	3’	GTTCTCCTGCTTGAGCTTCTGGTTGCTGTG	
NTCP	5’	AGCAAGATCAAGGCTCACTTCT	405
	3’	ATAGTGTGGCCTTTTGGACTTC	
MTP	5’	TTCTCTGCTTCTTCTCCTCCTA	403
	3’	GGCTCGTTTTCATAGGAGTAGA	
ApoA-I	5’	GGCAGAGACTATGTGTCCCAGTTTGA	564
	3’	GTCATCCAGCGCGGGTTTGGCCTTCTC	
ApoA-II	5’	ATAGTCTGCCATCATGAAGCTG	406
	3’	GAGAAAACAGGCAGAAGGTAGG	
ApoE	5’	CCGTGCTGTTGGTCACATT	1014
	3’	TTATTAAGCAAGGGCCACCA	